BTS guidelines for the management of malignant pleural effusions

G Antunes, E Neville, J Duffy, N Ali, on behalf of the BTS Pleural Disease Group, a subgroup of the BTS Standards of Care Committee

Thorax 2003;**58**(Suppl II):ii29–ii38

1 INTRODUCTION

The discovery of malignant cells in pleural fluid and/or parietal pleura signifies disseminated or advanced disease and a reduced life expectancy in cancer patients.[1] Median survival following diagnosis ranges from 3 to 12 months and is dependent on the stage and type of the underlying malignancy. The shortest survival time is observed in malignant effusions secondary to lung cancer and the longest in ovarian cancer, while malignant effusions due to an unknown primary have an intermediate survival time.[2–5]

Currently, lung cancer is the most common metastatic tumour to the pleura in men and breast cancer in women.[6] Together, both malignancies account for approximately 50–65% of all malignant effusions (table 1). Lymphomas, tumours of the genitourinary tract and gastrointestinal tract as a group account for a further 25%.[5 7–9] Pleural effusions from an unknown primary are responsible for 7–15% of all malignant pleural effusions.[5 7 8]

An algorithm for the management of malignant pleural effusions is shown in fig 1.

2 PATHOPHYSIOLOGY

The pleura consists of five main anatomical compartments (fig 2): the parietal systemic circulation (branches of the intercostal and internal mammary arteries), the parietal interstitial space, the pleural space lined on either side by mesothelial cells, the pulmonary interstitium, and the visceral circulation (bronchial and pulmonary arterioles).

Pleural fluid is filtered in the parietal pleural compartment from the systemic capillaries down a small pressure gradient into the pleural space. Under normal conditions the visceral pleura plays an insignificant role in pleural fluid turnover.[10]

Experiments using radioactive albumin and other labelled proteins have shown that pleural fluid secretion is greatest at the apex and absorption is increased towards the diaphragm and mediastinum.[11 12] Pleural fluid is drained out of the pleural space predominantly through the stomata of the parietal lymphatics lying between the parietal mesothelial cells. The number of parietal lymphatics is greatest at the diaphragm and mediastinum. These stomata merge into small lymphatic channels which, in turn, form larger vessels ultimately draining into the mediastinal lymph nodes.

Any disruption or obstruction by tumour cells along this intricate lymphatic network may result in a pleural effusion. This mechanism for pleural fluid accumulation has been confirmed by necroscopic studies which reveal that involvement of the regional lymph nodes is usually associated with the presence of a pleural effusion.[1 13] Typically, adenocarcinoma of the lung spreads to the parietal pleura from the visceral pleura along existing pleural adhesions. This is preceded by migration of tumour cells to the visceral pleura from underlying pulmonary capillaries—that is, haematogenous spread.[14] Pleural metastases from a primary site other than the lung result from haematogenous or lymphatic spread. Malignant effusions secondary to breast cancer arise either through chest wall lymphatics or via hepatic metastases resulting in either contralateral or bilateral effusions.[15]

Haemorrhagic malignant effusions usually result from invasion of blood vessels directly and/or tumour induced angiogenesis.[13] Vascular endothelial growth factor (VEGF), a cytokine possessing potent angiogenic activity and promoting endothelial permeability, may play a significant role in the formation of malignant effusions and local tumour growth.[16 17]

3 CLINICAL PRESENTATION

- **Massive pleural effusions are most commonly due to malignancy. [B]**
- **The majority of malignant effusions are symptomatic. [C]**

Massive pleural effusions, defined as complete or almost complete opacification of a hemithorax on

Table 1 Primary tumour site in patients with malignant pleural effusion

Primary tumour site	Salyer[7] (n=95)	Chernow[1] (n=96)	Johnston[8] (n=472)	Sears[2] (n=592)	Hsu[9] (n=785)	Total (%)
Lung	42	32	168	112	410	764 (37.5)
Breast	11	20	70	141	101	343 (16.8)
Lymphoma	11	–	75	92	56	234 (11.5)
GI tract	–	13	28	32	68	141 (6.9)
GU tract	–	13	57	51	70	191 (9.4)
Other	14	5	26	88	15	148 (7.3)
Unknown primary	17	13	48	76	65	219 (10.7)

GI=gastrointestinal; GU=genitourinary.

See end of article for authors' affiliations

Correspondence to: Dr G Antunes, Department of Respiratory Medicine, James Cook University Hospital, Marton Road, Middlesborough TS4 3BW, UK; george.antunes@stees.nhs.uk

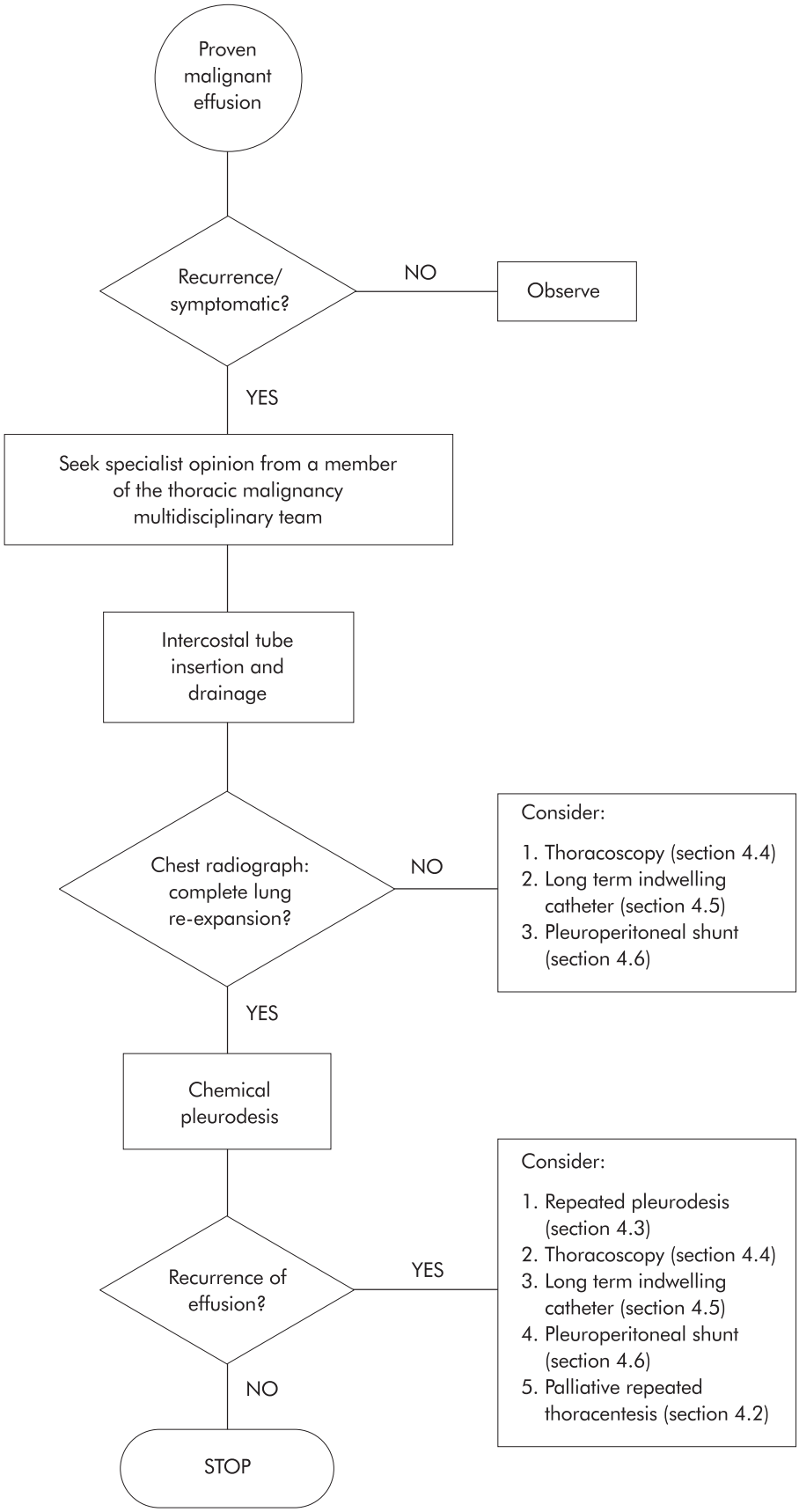

Figure 1 Algorithm for the management of malignant pleural effusions.

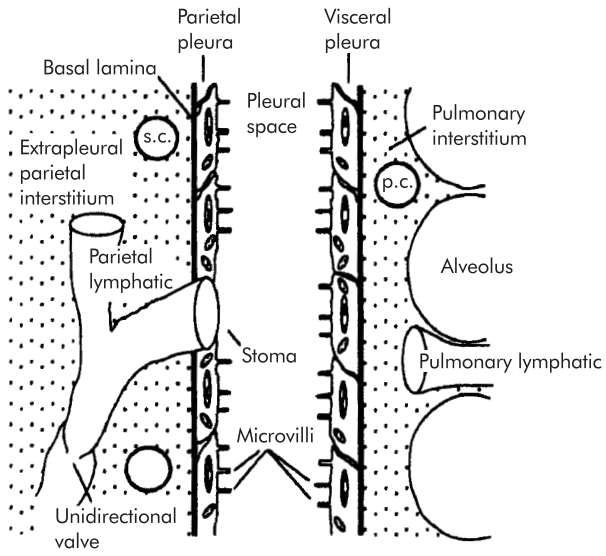

Figure 2 Schematic diagram of pleural anatomy; s.c.=systemic capillary; p.c.=pulmonary capillary. Modified from Miserocchi[10] with permission.

the chest radiograph, are more commonly associated with a malignant aetiology.[18] However, a modest number of patients (up to 25%) are asymptomatic at presentation—that is, they are found incidentally with physical examination or by chest radiography.[1] Dyspnoea is the most common presenting symptom and is occasionally accompanied by chest pain and cough. Dyspnoea is due to a combination of reduced compliance of the chest wall, depression of the ipsilateral diaphragm, mediastinal shift, and reduction in lung volume stimulating neurogenic reflexes. Chest pain is usually related to involvement of the parietal pleura, ribs, and other intercostal structures.[19] Constitutional symptoms including weight loss, malaise, and anorexia also generally accompany respiratory symptoms. The diagnosis of a malignant pleural effusion is discussed in the section on the investigation of a unilateral pleural effusion (page ii8).

4 MANAGEMENT OPTIONS

Treatment options for malignant pleural effusions are determined by several factors: symptoms and performance status of the patient, the primary tumour and its response to systemic therapy, and lung re-expansion following pleural fluid evacuation (table 2). Although small cell lung cancer, lymphoma, and breast cancer usually respond to chemotherapy, associated secondary pleural effusions may require intervention during the course of treatment. Common and less common management options will be discussed below.

4.1 Observation

- **Observation is recommended if the patient is asymptomatic or there is no recurrence of symptoms after initial thoracentesis. [C]**
- **Advice should be sought from the thoracic malignancy multidisciplinary team for symptomatic or recurrent malignant effusions. [C]**

The majority of these patients will become symptomatic in due course and require further intervention. There is no evidence that initial thoracentesis carried out according to standard technique will reduce the chances of subsequent effective pleurodesis.

4.2 Therapeutic pleural aspiration

- **Repeat pleural aspiration is recommended for the palliation of breathlessness in patients with a very short life expectancy. [C]**
- **Caution should be taken if removing more than 1.5 l on a single occasion. [C]**
- **The recurrence rate at 1 month after pleural aspiration alone is close to 100%. [B]**
- **Intercostal tube drainage without pleurodesis is not recommended because of a high recurrence rate. [B]**

Repeated therapeutic pleural aspiration provides transient relief of symptoms and avoids hospitalisation for patients with limited survival expectancy and poor performance status. This option is appropriate for frail or terminally ill patients but individual patient preference may also dictate its use in patients who have had a previous failed intercostal tube and pleurodesis.[20] The amount of fluid evacuated will be guided by patient symptoms (cough, chest discomfort) and should be limited to 1–1.5 l (see section 4.3.2). Pleural aspiration alone and intercostal tube drainage without instillation of a sclerosant are associated with a high recurrence rate and a small risk of iatrogenic pneumothorax and empyema.[21–26]

4.3 Intercostal tube drainage and intrapleural instillation of sclerosant

Pleurodesis requires a diffuse inflammatory reaction and local activation of the coagulation system with fibrin deposition.[27] Antony and colleagues have demonstrated increased growth factor-like activity in mesothelial cells exposed to tetracycline leading to fibroblast proliferation. This activity gradually decays once the tetracycline is removed.[28] Increased pleural fibrinolytic activity is associated with failure of pleurodesis. Rodriguez-Panadero showed that rapid reduction in fibrinolytic activity within 24 hours using pleural D-dimer levels was

Table 2 Treatment options for malignant pleural effusions

	Management approach	Advantages	Disadvantages
Commonly used options	Observation	Indicated for small and asymptomatic effusions	Effusions will usually increase in size and need intervention
	Therapeutic thoracentesis	Transient and rapid relief of dyspnoea; minimally invasive; suitable for outpatient setting	High recurrence rate; risk of iatrogenic empyema and pneumothorax
	Chest tube insertion with intrapleural sclerosant	Success rate >60%; low incidence of complications	Side effects of sclerosants (see text)
	Thoracoscopy with talc poudrage	High success rate (90%)	Invasive procedure and may be unavailable
Less commonly used options	Long term indwelling catheter drainage	Suitable for outpatient setting; modest success rate	Local infection; risk of tumour seeding in mesothelioma
	Pleuroperitoneal shunt	Useful for intractable effusions and trapped lung	Good performance status required to manage shunt (WHO 0,1); occlusion; infection
	Pleurectomy	Very low recurrence rate	Invasive procedure; significant morbidity and mortality

Box 1 Chemical pleurodesis

(1) Insert small bore intercostal tube (10–14 F).
(2) Controlled evacuation of pleural fluid.
(3) Confirm full lung re-expansion and position of intercostal tube with chest radiograph.
(4) Administer premedication prior to pleurodesis.
(5) Instill lignocaine solution (3 mg/kg; maximum 250 mg) into pleural space followed by sclerosant of choice (for sclerosants, see text).
(6) Clamp tube for 1 hour and consider patient rotation for talc slurry.
(7) Remove intercostal tube within 12–72 hours if lung remains fully re-expanded and there is satisfactory evacuation of pleural fluid.

associated with good outcome of talc pleurodesis. In contrast, the group in whom the D-dimer level took longer to return to baseline (>24 hours) had a greater number of treatment failures.[29]

In animals the effectiveness of pleurodesis may be reduced by concomitant use of corticosteroids. Recent evidence in rabbits has shown reduced pleural inflammatory reaction and, in some cases, prevention of pleurodesis with administration of corticosteroids at the time of talc pleurodesis.[30] The administration of non-steroidal anti-inflammatory agents at the time of pleurodesis is more contentious and, at present, evidence against their use is lacking.

Belani and colleagues, using a simulation model, compared the cost effectiveness of intercostal tube insertion and chemical pleurodesis (tetracycline, doxycyline and bleomycin) with operative talc poudrage. The cost of symptom free days was used to determine cost effectiveness. Intercostal tube insertion and chemical pleurodesis was found to be more cost effective than talc poudrage where theatre time and personnel contributed significantly to the extra cost.[31] The method of chemical pleurodesis will be discussed below and is summarised in box 1.

4.3.1 Size of intercostal tube

- **Small bore (10–14 F) intercostal catheters should be the initial choice for effusion drainage and pleurodesis. [B]**

Conventional large bore intercostal tubes (24–32 F) have been employed in most studies involving sclerosing agents.[32] They have traditionally been used because they are thought to be less prone to obstruction by clots, but there is little published evidence to confirm this. The placement of large bore tubes is perceived to be associated with significant discomfort[33] and this has led to the assessment of smaller bore tubes (10–14 F) for the drainage and administration of sclerosing agents. Studies using small bore intercostal tubes with commonly used sclerosants have reported similar success rates to large bore tubes.[34–38] The small bore tubes in these studies were inserted either at the patient's bedside by a physician or under radiological guidance.

Comparison between small bore and large bore intercostal tubes has been considered in two studies. Clementsen *et al*,[38] in a randomised study using tetracycline as a sclerosing agent, compared a small bore tube (10 F) placed at bedside with a large bore tube (24 F). Although no significant difference in success rate was observed between the two groups, the small bore catheter was associated with less discomfort. Small bore tubes (10 F) were also considered more successful than large bore tubes (32–38 F) in a non-randomised study .[34] Both studies recruited only a small number of patients and larger randomised studies are necessary to support these findings.

Small bore tubes have been used for ambulatory or outpatient pleurodesis. Patz *et al*[39] used a fluoroscopically placed tube (10 F) connected to a closed gravity drainage bag system for this purpose. Bleomycin was the preferred sclerosing agent and the pleurodesis success rate approached 80%. Six patients complained of mild chest pain during insertion of the intercostal tube. Two of the intercostal tubes became blocked but were successfully cleared with a guidewire.

In view of the potential advantages (reduced patient discomfort, ease of placement, and comparable pleurodesis success rates), small bore tubes (10–14 F) should be considered initially for the drainage of malignant effusions.

4.3.2 Lung re-expansion, fluid drainage, and suction

- **Large pleural effusions should be drained in a controlled fashion to reduce the risk of re-expansion pulmonary oedema (RPO). [C]**
- **Suction to aid pleural drainage before and after pleurodesis is usually unnecessary but, if applied, a high volume, low pressure system is recommended. [C]**
- **In patients where only partial pleural apposition can be achieved, chemical pleurodesis should still be attempted and may provide symptomatic relief. [B]**
- **Once effusion drainage and lung re-expansion have been radiographically confirmed, pleurodesis should not be delayed while the cessation of pleural fluid drainage is awaited. [B]**

The most important requirement for successful pleurodesis is satisfactory apposition of the parietal and visceral pleura, confirmed radiologically.[32 40 41] Incomplete lung re-expansion may be due to a thick visceral peel ("trapped lung"), pleural loculations, proximal large airway obstruction, or a persistent air leak. Most studies indicate that the lack of a response following instillation of a sclerosant is predominantly due to incomplete lung expansion.[41 42] Where complete lung re-expansion or pleural apposition is not achieved and the patient is unsuitable for surgical intervention, pleurodesis should still be attempted. Robinson and colleagues,[43] in a study using doxycycline as a sclerosing agent, reported a favourable response in nine out of 10 patients with partial re-expansion of the lung.

The amount of pleural fluid drained per day before the instillation of a sclerosant (<150 ml/day) is less relevant for successful pleurodesis than radiographic confirmation of fluid evacuation and lung re-expansion. In a randomised study, a shorter period of intercostal tube drainage and hospital stay was seen in the group in whom sclerotherapy was undertaken as soon as complete lung re-expansion was documented (majority <24 hours) than in the group in whom pleurodesis was attempted only when the fluid drainage was <150 ml/day. The success rate in both groups approached 80%.[41]

Large pleural effusions should be drained in a controlled fashion avoiding evacuation of more than 1–1.5 l at one time or slowed to about 500 ml/hour, and aspiration discontinued if the patient develops chest discomfort, persistent cough, or vasovagal symptoms. Re-expansion pulmonary oedema (RPO) is a well described but rare complication following rapid expansion of a collapsed lung through evacuation of large amounts of pleural fluid at a single time and the use of early and excessive pleural suction.[44 45] Putative pathophysiological mechanisms include reperfusion injury of the underlying hypoxic lung, increased capillary permeability, and local production of neutrophil chemotactic factors such as interleukin (IL)-8.[46] Suction may be required for incomplete lung expansion and a persistent air leak. When suction is applied, the use of high volume, low pressure systems is recommended with a gradual increment in pressure to about –20 cm H_2O.

4.3.3 Analgesia and premedication

- **Lignocaine (3 mg/kg; maximum 250 mg) should be administered intrapleurally just prior to sclerosant administration. [B]**

Table 3 Sclerosing agents available in UK

Sclerosing agent	Recommended dose	Average success rate	Common side effects	Serious complications	Approx cost per treatment	Manufactured in UK	No of treatments
Tetracycline	1–1.5 g	65%[49 53–55]	Chest pain, fever, cough	None	1.5 g: £13.95†	No	1
Sterile talc (slurry or poudrage)	2–5 g	90%[42 64 65 68]	Chest pain, fever	Respiratory failure/ARDS	5 g: £1.60	Yes*	1
Bleomycin	60 units	61%[56 67 72–74]	Chest pain, fever, nausea	None	60 units: £68.75	Yes	1
Doxycycline	500 mg	76%[43 47 78 79]	Chest pain, fever	None	500 mg: £29.50	No‡	>1

ARDS=adult respiratory distress syndrome.
*Produced in Germany and available via international wholesalers.
†Produced under manufacturer's licence in UK.
‡Not available or licensed for use in the UK.

- **Premedication should be considered to alleviate anxiety and pain associated with pleurodesis. [C]**

Intrapleural administration of sclerosing agents is associated with chest pain and the incidence varies from 7% in the case of talc to 40% with doxycycline.[43 47] Lignocaine is the best studied local anaesthetic for intrapleural administration. The onset of action of lignocaine is almost immediate and it should therefore be administered just before the sclerosant. The issue of safety has been highlighted in two studies. Wooten *et al*[48] showed that the mean peak serum concentration of lignocaine following 150 mg of intrapleural lignocaine was 1.3 μg/ml, well below the serum concentration associated with central nervous system side effects (that is >3 μg/ml). In an earlier study of 20 patients larger doses of lignocaine were necessary to achieve acceptable levels of local anaesthesia. The patients receiving 250 mg lignocaine had more frequent pain-free episodes than those given 200 mg, while serum levels remained within the therapeutic range. Side effects were limited to transient paraesthesia in a single patient.[49] The reason for the significant difference in analgesia between the two groups with only a small increment in the lignocaine dose was unclear.

In the context of pleurodesis, premedication and sedation is poorly studied and no evidence based guidelines exist. Pleurodesis is an uncomfortable procedure and is associated with anxiety for the patient. The use of sedation may be helpful to allay such fears and induce amnesia. The level of sedation using either an opioid (with a suitable anti-emetic) or benzodiazepine should be appropriate—that is, maintenance of verbal communication and cooperation. Sedation employed before pleurodesis should be conducted with continuous monitoring with pulse oximetry and in a setting where resuscitation equipment is available.[50]

4.3.4 Selecting a sclerosing agent

- **Talc is the most effective sclerosant available for pleurodesis. [B]**
- **A small number of patients (<1%) may develop acute respiratory failure following talc administration. [B]**
- **Tetracycline is modestly effective, has few severe side effects, and is the preferred sclerosant to minimise adverse event rates. [B]**
- **Bleomycin is an alternative sclerosant with a modest efficacy rate but is expensive. [B]**
- **Pleuritic chest pain and fever are the most common side effects of sclerosant administration. [B]**

Despite the evaluation of a wide variety of agents, to date no ideal sclerosing agent exists. Comparison of sclerosing agents is hampered by the lack of comparative randomised trials, different eligibility criteria, and disparate criteria for measuring response and end points. A complete response is usually defined as no re-accumulation of pleural fluid after pleurodesis until death, and a partial response as partial re-accumulation of fluid radiographically but not requiring further pleural intervention such as aspiration. An ideal sclerosing agent must possess several essential qualities: a high molecular weight and chemical polarity, low regional clearance, rapid systemic clearance, a steep dose-response curve, and be well tolerated with minimal or no side effects. The choice of a sclerosing agent will be determined by the efficacy or success rate of the agent, accessibility, safety, ease of administration, number of administrations to achieve a complete response, and cost (table 3). Sclerosing agents available for routine use will be discussed first.

Tetracycline

Until recently, tetracycline had been the most popular and widely used sclerosing agent in the UK.[51] The manufacturer of parenteral tetracycline discontinued production and distribution of the agent in the US in 1993 and a similar fate may follow in the UK.[52] However, currently the parenteral preparation is available in Germany and may be imported via international wholesalers. These suppliers state that supplies are expected to remain available for the foreseeable future. The advantages of tetracycline are its reasonable efficacy, excellent safety profile, ease of administration, and low cost. Success rates (complete and partial response rates) from the larger studies have varied from 50% to 92% with a mean of 65%.[41 49 53–55] Side effects include fever (10%) and pleuritic chest pain (30%), which are usually transient and respond readily to antipyretics and analgesia. The optimal dose for intrapleural administration is 1.0–1.5 g or 20 mg/kg. Studies using smaller doses such as 500 mg have reported lower response rates, while there is no evidence to support the use of larger doses of tetracycline.[56 57]

Thoracoscopic instillation of tetracycline has been studied in two randomised trials for malignant effusions in breast cancer. Evans *et al* compared thoracoscopic instillation of 500 mg tetracycline with 1.5 g via chest tube. The complete response rate at 1 month for both groups was 76%.[58] Fentiman *et al*,[59] on the other hand, compared talc poudrage with thoracoscopically administered tetracycline (500 mg). The talc group was found to be superior with a successful palliation at 1 month of 92% compared with 48% for the tetracycline group. Tetracycline pleurodesis may also be attempted using a needle aspiration technique where the agent is administered after draining an effusion to dryness. A recent randomised study employing this method reported a disappointingly low pleurodesis success rate of 29% at 6 weeks compared with 80% with intercostal tube drainage.[60]

Sterile talc

Talc ($Mg_3Si_4O_{10}(OH)_2$) is a trilayered magnesium silicate sheet that is inert and was first used as a sclerosing agent in 1935.[61] Talc used for intrapleural administration is asbestos-free and sterilised effectively by dry heat exposure, ethylene oxide, and

gamma radiation. It may be administered in two ways: at thoracoscopy using an atomiser termed "talc poudrage" or via an intercostal tube in the form of a suspension termed "talc slurry".[62 63]

Success rates (complete and partial response) for talc slurry range from 88% to 100% with a mean of 90%.[24 42 64 65] The majority of studies have used talc slurry alone and only a limited number of comparative studies have been published. A truncated randomised study by Lynch and colleagues[66] compared talc slurry (5 g) with bleomycin (60 units) and tetracycline (750 mg). Although the study was terminated early because of the removal of tetracycline from the US market, analysis of the data to that point revealed no differences between the three treatment groups 1 month after pleurodesis. In a recent randomised trial between talc slurry (5 g) and bleomycin (60 units), 90% of the talc group achieved a complete response at 2 weeks compared with 79% of the bleomycin group, which was statistically insignificant.[67] Yim *et al*[68] compared talc slurry (5 g) with talc poudrage (5 g) and found no significant difference between the two groups with respect to complete response rate (both over 90%), chest drainage duration, length of hospital stay, and complication rate.

Talc slurry is usually well tolerated and pleuritic chest pain and mild fever are the most common side effects observed. A serious complication associated with the use of talc is adult respiratory distress syndrome (ARDS) or acute pneumonitis leading to acute respiratory failure. The mechanism of acute talc pneumonitis is unclear and has been reported with both talc poudrage and slurry.[42 69] The dose of talc and the physical characteristics (size and type) appear to be the most important determinants for the development of this complication.[70] In a case series reported by Kennedy *et al*[42] five patients developed respiratory failure with talc slurry pleurodesis (10 g). Three patients required mechanical ventilation but were later successfully extubated. Studies using lower doses (2–5 g) have reported excellent complete response rates with a lower incidence of serious adverse effects including acute respiratory failure.[64 65] The diagnosis of talc pneumonitis is made after exclusion of other possible mechanisms for pulmonary infiltrates and respiratory failure—that is, re-expansion pulmonary oedema and lymphangitis carcinomatosa.

Bleomycin

Bleomycin is the most widely used antineoplastic agent for the management of malignant pleural effusions. Its mechanism of action is predominantly as a chemical sclerosant similar to talc and tetracycline. Although 45% of the administered bleomycin is absorbed systemically, it has been shown to cause minimal or no myelosuppression.[71] Bleomycin is an effective sclerosant with success rates after a single administration ranging from 58% to 85% with a mean of 61%.[56 67 72–74] Large comparative trials have found it to be superior to tetracycline.[56 74 75] It has an acceptable side effect profile with fever, chest pain, and nausea the most common adverse effects. The recommended dose is 60 units mixed in normal saline. Bleomycin has also been used in studies evaluating small bore intercostal tubes placed under radiological guidance with similar efficacy rates.[37 39 76 77] The major disadvantages of bleomycin are the cost per treatment compared with other sclerosants and that it needs to be performed by trained personnel familiar with the administration of cytotoxic drugs (table 3).

Rarely used and historical agents

(1) Doxycyline: Although doxycycline is widely used in the US and is available in Continental Europe, it is not available or licensed for intrapleural administration in the UK. It has been evaluated in several small trials with success rates varying from 65% to 100% with a mean of 76%.[43 47 78 79] All but one of the trials used a dose of 500 mg mixed in normal saline. Prevost *et al*[80] used doses in excess of 2 g with a reported success rate of 82%. Side effects are similar to those with tetracycline—that is, fever (30%) and mild to moderate pleuritic chest pain (up to 60%). Doxycycline has been used with small bore tubes in two studies. Patz *et al*[37] in a large randomised study compared bleomycin with doxycycline (500 mg) in 106 patients. The complete response rate at 1 month for doxycycline was 79%. In a similar study, Seaton *et al*[36] reported a complete response rate of 81% with a low incidence of side effects. The major disadvantage of doxycycline is the need for repeated instillations to obtain a satisfactory success rate. This may lead to prolonged catheter or intercostal tube indwelling times with a potential increase in infection, patient discomfort, and overall cost in treatment.

(2) Minocycline: Minocycline has been used as a sclerosing agent but experience in humans is limited to a single small and uncontrolled study.[81] A recent study in rabbits suggests that it may be as effective as tetracycline at inducing pleurodesis.[82] Minocycline is not available or licensed for intrapleural administration in the UK.

(3) Other sclerosants: *Corynebacterium parvum* extract,[83–89] interferons (interferon-α and -β),[90–94] interleukins (IL-2),[95 96] and several chemotherapeutic drugs (cisplatin, cytosine arabinoside, and mitoxantrone)[97–99] have been used for pleurodesis with variable and usually disappointing efficacy rates. Most of the trials have been uncontrolled and recruited small numbers of patients. *Corynebacterium parvum*, interferons, and interleukins require multiple administrations, while significant toxicity is encountered with the use of the chemotherapeutic drugs.

4.3.5 Rotation following pleurodesis

- **Patient rotation is not necessary after intrapleural instillation of tetracycline class agents. [A]**

Rotation of the patient following intrapleural administration of a sclerosing agent is described in most pleurodesis studies in order to achieve adequate distribution of the agent over the pleura. However, patient rotation is time consuming and may cause further discomfort for these patients. A study using radiolabelled tetracycline has shown that tetracycline is dispersed throughout the pleural space within seconds and rotation of the patient did not influence the distribution of the agent.[100] A subsequent randomised trial using tetracycline, minocycline, and doxycycline revealed no significant difference in the success rate of the procedure or duration of fluid drainage between the rotation and non-rotation groups.[101] Patient rotation is still required when using talc slurry until further evidence is available.

4.3.6 Clamping of intercostal tube

- **The intercostal tube should be clamped for 1 hour after sclerosant administration. [C]**
- **In the absence of excessive fluid drainage (>250 ml/day) the intercostal tube should be removed within 12–72 hours of sclerosant administration. [C]**

Clamping of the intercostal tube following intrapleural administration of the sclerosant should be brief (1 hour). This will prevent the sclerosant from immediately draining back out of the pleural space, although this may not be important.[100] Intercostal tube removal has been recommended when fluid drainage reached less than 150 ml/day, but there is a lack of evidence to support this action.[102–104] In the absence of any evidence that protracted drainage is beneficial, and given the discomfort associated with prolonged drainage, we arbitrarily recommend removal of the intercostal tube within 12–72 hours after the instillation of the sclerosant provided the lung remains fully re-expanded and there is satisfactory evacuation of pleural fluid on the chest radiograph. Where excessive fluid drainage persists (>250 ml/day), repeat pleurodesis may be attempted with an alternative sclerosant. In

the event of incomplete lung expansion any treatable cause for this should be excluded and the drain may then be removed as pleurodesis is unlikely to succeed.

4.3.7 Malignant seeding at intercostal tube or port site

- **Patients with proven or suspected mesothelioma should receive prophylactic radiotherapy to the site of biopsy or chest drain insertion. [A]**

Local tumour recurrence or seeding following diagnostic and therapeutic pleural aspiration, pleural biopsy, intercostal tube insertion, and thoracoscopy is uncommon in non-mesothelioma malignant effusions.[105–108] However, in mesothelioma 40% of patients may develop malignant seeding at the site of diagnostic pleural procedures. In a randomised study Boutin *et al*[109] found that local metastases were prevented in patients who received radiotherapy to the thoracoscopic tract site. All the patients received radiotherapy within 2 weeks of thoracoscopy. It should be noted that further clinical trials of procedure site radiotherapy in mesothelioma are currently recruiting. The role of prophylactic radiotherapy following pleural procedures in non-mesothelioma malignant effusions has not been established and therefore cannot be recommended.

4.3.8 Intrapleural fibrinolytics

- **Intrapleural instillation of fibrinolytic drugs is recommended for the relief of distressing dyspnoea due to multiloculated malignant effusion resistant to simple drainage. [C]**

The use of fibrinolytic agents represents an advance in the management of multiloculated malignant effusions. Immune mediated or haemorrhagic complications have rarely been described with the administration of intrapleural fibrinolytics in contrast to systemic administration of these agents.[110 111]

Jerjes-Sanchez *et al*[112] administered intrapleural streptokinase (250 000 IU) in an open study to four patients with multiloculated malignant effusions not considered suitable for pleurodesis at the time. In three of the four patients fibrinolytic administration allowed radiographic improvement and led to successful pleurodesis. A more recent study found that intrapleural streptokinase increased pleural fluid drainage and led to radiographic improvement and amelioration of symptoms in 10 patients with multiloculated or septated malignant effusions. Intrapleural streptokinase was well tolerated and no allergic or haemorrhagic complications were reported.[113] Gilkeson *et al*[114] preferred urokinase in their prospective but non-randomised study. Twenty two malignant pleural effusions were treated with urokinase resulting in substantial increase in pleural fluid output in patients both with and without radiographic evidence of loculations. The majority then underwent pleurodesis with doxycycline resulting in a complete response rate of 56%. Similarly, no allergic or haemorrhagic complications were encountered.

None of these studies is large enough to accurately describe the safety profile of fibrinolytic drugs in this setting. The physician should therefore use these agents with caution, carefully considering the risk/benefit balance for the individual patient. An appropriately experienced specialist should be involved in the care of all patients receiving this treatment.

4.4 Thoracoscopy in malignant pleural effusion

- **Thoracoscopy should be considered for the diagnosis of suspected but unproven malignant pleural effusion. [B]**
- **Thoracoscopy should be considered for the control of recurrent malignant pleural effusion. [B]**
- **Thoracoscopy is a safe procedure with low complication rates. [B]**

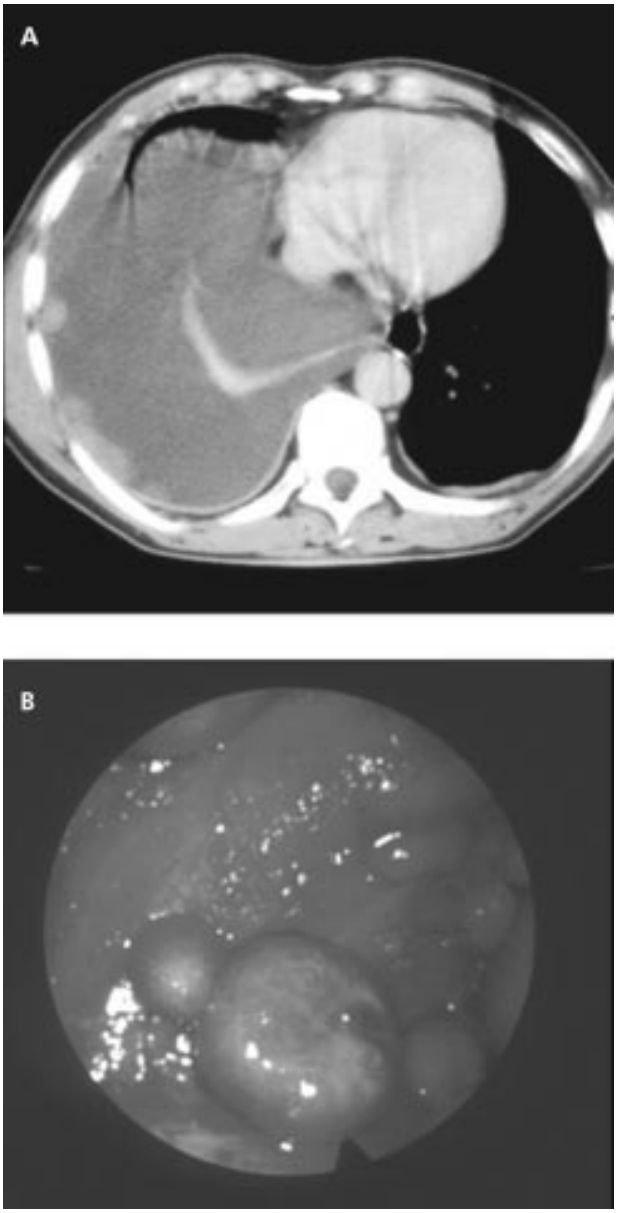

Figure 3 (A) CT scan and (B) thoracoscopic appearance of pleural malignancy (breast carcinoma metastases).

Thoracoscopy (under sedation or general anaesthesia) has grown in popularity as a diagnostic and therapeutic tool for malignant effusions.[115–117] The thoracoscopic appearance of pleural malignancy and a thoracic CT scan from the same patient are shown in fig 3. The diagnostic yield and accuracy of thoracoscopy for malignant effusions is greater than 90%.[55 117 118] Patients with exudative pleural effusions of unknown aetiology after pleural fluid cytological and microbiological examination should proceed to pleural tissue biopsy (see guideline on the investigation of pleural effusions, page ii8).

The therapeutic role of thoracoscopy has been evaluated extensively. Talc poudrage is an effective method for controlling malignant effusions with a mean pleurodesis success rate of more than 90%.[115 116 119 120] Patient selection for thoracoscopy and talc poudrage is important in view of the invasive nature of the procedure and cost. The role of surgical thoracoscopy in patients with trapped lung is less clear. The procedure can facilitate breaking up of loculations and release of adhesions

and thereby aid lung re-expansion and apposition of the pleura for talc poudrage.[121]

Thoracoscopy is a safe and well tolerated procedure with a low perioperative mortality rate (<0.5%).[116 122] The most common major complications are empyema and acute respiratory failure secondary to infection or re-expansion pulmonary oedema.[115 123]

4.5 Long term indwelling pleural catheter drainage

- **Chronic indwelling pleural catheters are effective in controlling recurrent and symptomatic malignant effusions in selected patents. [B]**

Insertion of a long term tunnelled pleural catheter is an alternative method for controlling recurrent and symptomatic malignant effusions including patients with trapped lung. A specific catheter has been developed for this purpose and the published studies employing this catheter have reported encouraging results.[124 125]

In the only randomised and controlled study to date, Putnam and colleagues[124] compared a long term indwelling pleural catheter with doxycycline pleurodesis via a standard intercostal tube. The length of hospitalisation for the indwelling catheter group was significantly shorter (1 day) than that of the doxycycline pleurodesis group (6 days). Spontaneous pleurodesis was achieved in 42 of the 91 patients in the indwelling catheter group. A late failure rate (defined as reaccumulation of pleural fluid after initial successful control) of 13% was reported compared with 21% for the doxycycline pleurodesis group. There was a modest improvement in the quality of life and dyspnoea scores in both groups. The complication rate was higher (14%) in the indwelling catheter group and included local cellulitis (most common) and, rarely, tumour seeding of the catheter tract.

An indwelling pleural catheter is therefore an effective option for controlling recurrent malignant effusions when length of hospitalisation is to be kept to a minimum (reduced life expectancy) and expertise and facilities exist for outpatient management of these catheters.

4.6 Pleuroperitoneal shunting

- **Pleuroperitoneal shunts are an alternative and effective option in patients with a trapped lung or failed pleurodesis. [B]**

In selected patients with trapped lung and large effusions refractory to chemical pleurodesis, pleuroperitoneal shunting is an acceptable palliative option. The shunt consists of a valved chamber (containing two unidirectional valves) with fenestrated pleural and peritoneal catheters attached at either end. The device is pressure activated but spontaneous flow will also occur when the pressure gradient between the pleural and peritoneal space is more than 1 cm H_2O. More often the pressure gradient is low and requires manual compression of the pump chamber percutaneously, sometimes over 400 times per day.[126 127] The insertion of the shunt is facilitated by thoracoscopy or a mini-thoracotomy and the duration of hospital stay varies between 4 and 6 days. The procedure is usually well tolerated and postoperative morbidity and mortality are low.[128]

Complications include shunt occlusion, infection, and tumour seeding or implantation into the peritoneal cavity. Shunt occlusion rates vary from 12% to 25% and normally requires replacement of the shunt.[128 129] The presence of pleural infection, multiple pleural loculations, and inability to compress the pump chamber are contraindications to pleuroperitoneal shunting.

4.7 Pleurectomy

Pleurectomy is an effective but invasive method for treating malignant pleural effusions. Complications may include empyema, haemorrhage, and cardiorespiratory failure (operative mortality rates of 10–13%). Patient selection is therefore important and this method should be reserved for those who have failed to respond to other forms of treatment.[130 131] The advent of video assisted thoracic surgery (VATS) has enabled parietal pleurectomy to be performed without a formal thoracotomy. A study of 19 patients (13 with mesothelioma, six with metastatic adenocarcinoma) found this thoracoscopic method to be safe and associated with an effusion recurrence rate of 10%. The median postoperative stay was 5 days and all patients were discharged home.[132]

Audit points

- Performance status at time of chemical pleurodesis.
- Use of small bore catheters in the management of malignant pleural effusions.
- Assessment of lung re-expansion prior to pleurodesis.
- Assessment of pain during and after pleurodesis using a pain scale or score.
- Complete and partial response rates of sclerosing agents.
- Surgical referral rates for the management of malignant pleural effusions.

Future potential areas for research

- Large prospective randomised trials comparing small bore catheters and large bore intercostal tubes for pleural fluid drainage and pleurodesis in malignant pleural effusions.
- Role of premedication before pleurodesis in malignant pleural effusion.
- Clinical trials of promising new sclerosants such as transforming growth factor beta (TGFβ) and iodopovidone.
- Place of suction after pleurodesis in terms of duration of fluid drainage and length of hospital stay.

Authors' affiliations
G Antunes, Department of Respiratory Medicine, James Cook University Hospital, Middlesborough TS4 3BW, UK
E Neville, Respiratory Centre, St Mary's Hospital, Portsmouth PO3 6AD, UK
J Duffy, Cardiothoracic Surgery Department, Nottingham City Hospital, Nottingham NG5 1PB, UK
N Ali, Kings Mill Centre, Sutton in Ashfield, Nottingham NG17 4LJ, UK

REFERENCES

1 **Chernow B**, Sahn SA. Carcinomatous involvement of the pleura. *Am J Med* 1977;**63**:695–702. [**IV**]
2 **Sears D**, Hajdu SI. The cytologic diagnosis of malignant neoplasms in pleural and peritoneal effusions. *Acta Cytol* 1987;**31**:85–97. [**III**]
3 **Molengraft van de FJJM**, Vooijs GP. Survival of patients with malignancy-associated effusions. *Acta Cytol* 1989;**33**:911–6. [**III**]
4 **Bonnefoi H**, Smith IE. How should cancer presenting as a malignant effusion be managed? *Br J Cancer* 1996;**74**:832–5. [**IV**]
5 **Abbruzzese JL**, Abbruzzese MC, Hess KR, *et al*. Unknown primary carcinoma: natural history and prognostic factors in 657 consecutive patients. *J Clin Oncol* 1994;**12**:1272–80. [**III**]
6 **DiBonito L**, Falconieri G, Colautti I, *et al*. The positive pleural effusion. A retrospective study of cytopathologic diagnoses with autopsy confirmation. *Acta Cytol* 1992;**36**:329–32. [**III**]
7 **Salyer WR**, Eggleston JC, Erozan YS. Efficacy of pleural needle biopsy and pleural fluid cytopathology in the diagnosis of malignant neoplasm involving the pleura. *Chest* 1975;**67**:536–9. [**III**]
8 **Johnston WW**. The malignant pleural effusion. A review of cytopathologic diagnoses of 584 specimens from 472 consecutive patients. *Cancer* 1985;**56**:905–9. [**III**]
9 **Hsu C**. Cytologic detection of malignancy in pleural effusion: a review of 5255 samples from 3811 patients. *Diagn Cytopathol* 1987;**3**:8–12. [**III**]
10 **Miserocchi G**. Physiology and pathophysiology of pleural fluid turnover. *Eur Respir J* 1997;**10**:219–25. [**IV**]
11 **Negrini D**, Pistolesi M, Miniati M, *et al*. Regional protein absorption rates from the pleural cavity in dogs. *J Appl Physiol* 1985;**58**:2062–7. [**III**]
12 **Miserocchi G**, Venturoli D, Negrini D, *et al*. Intrapleural fluid movements described by a porous flow model. *J Appl Physiol* 1992;**73**:2511–6. [**IIb**]

13 **Meyer PC**. Metastatic carcinoma of the pleura. *Thorax* 1966;**21**:437–43. [**III**]
14 **Rodriguez-Panadero F**, Naranjo FB, Lopez-Mejias J. Pleural metastatic tumours and effusions. Frequency and pathogenic mechanisms in a post-mortem series. *Eur Respir J* 1989;**2**:366–9. [**III**]
15 **Fentiman IS**, Reubens RD, Hayward JL. Control of pleural effusions in patients with breast cancer. A randomized trial. *Cancer* 1983;**2**:737–9. [**Ib**]
16 **Kraft A**, Weindel K, Ochs A, *et al*. Vascular endothelial growth factor in the sera and effusions of patients with malignant and nonmalignant disease. *Cancer* 1999;**85**:178–87. [**III**]
17 **Hott JW**, Yu L, Antony VB, *et al*. Role of vascular endothelial growth factor (VEGF) in the formation of malignant pleural effusions. *Am J Respir Crit Care Med* 1999;**159**:A212. [**III**]
18 **Maher GG**, Berger HW. Massive pleural effusion: malignant and nonmalignant causes in 46 patients. *Am Rev Respir Dis* 1972;**105**:458–60. [**III**]
19 **Judson MA**, Sahn SA. Pulmonary physiologic abnormalities caused by pleural disease. *Semin Respir Crit Care Med* 1995;**16**:346–53. [**IV**]
20 **Stretton F**, Edmonds P, Marrinan M. Malignant pleural effusions. *Eur J Palliative Care* 1999;**6**:5–9. [**IV**]
21 **Lambert C**, Shah HH, Urschel HC Jr, *et al*. The treatment of malignant pleural effusions by closed trocar tube drainage. *Ann Thorac Surg* 1967;**3**:1–5. [**IIb**]
22 **Anderson CB**, Philpott GW, Ferguson TB. The treatment of malignant effusions. *Cancer* 1974;**33**:916–22. [**III**]
23 **Sorensen PG**, Svendsen TL, Enk B. Treatment of malignant pleural effusion with drainage, with and without instillation of talc. *Eur J Respir Dis* 1984;**65**:131–5. [**Ib**]
24 **Groth G**, Gatzemeier U, Haubingen K, *et al*. Intrapleural palliative treatment of malignant pleural effusions with mitoxantrone versus placebo (pleural tube alone). *Ann Oncol* 1991;**2**:213–5. [**Ib**]
25 **Izbicki R**, Weyhing BT, Baker L, *et al*. Pleural effusion in cancer patients. A prospective randomized study of pleural drainage with the addition of radioactive phosphorus to the pleural space versus pleural drainage alone. *Cancer* 1975;**36**:1511–8. [**Ib**]
26 **Zaloznik AJ**, Oswald SG, Langin M. Intrapleural tetracycline in malignant pleural effusions. *Cancer* 1983;**51**:752–5. [**Ib**]
27 **Antony VB**. Pathogenesis of malignant pleural effusions and talc pleurodesis. *Pneumologie* 1999;**10**:493–8. [**IV**]
28 **Antony VB**, Rothfuss KJ, Godbey SW, *et al*. Mechanism of tetracycline-hydrochloride-induced pleurodesis. *Am Rev Respir Dis* 1992;**146**:1009–13. [**III**]
29 **Rodriguez-Panadero F**, Segado A, Juan JM, *et al*. Failure of talc pleurodesis is associated with increased pleural fibrinolysis. *Am J Respir Crit Care Med* 1995;**151**:785–90. [**IIb**]
30 **Xie C**, Teixeira LR, McGovern JP, *et al*. Systemic corticosteroids decrease the effectiveness of talc pleurodesis. *Am J Respir Crit Care Med* 1999;**157**:1441–4. [**IIa**]
31 **Belani CP**, Einarson TR, Arikian SR, *et al*. Cost-effectiveness analysis of pleurodesis in the management of malignant pleural effusion. *J Oncol Manag* 1995;**4**:24–34. [**IIb**]
32 **Hausheer FH**, Yarbro JW. Diagnosis and treatment of malignant pleural effusion. *Semin Oncol* 1985;**12**:54–75. [**IV**]
33 **Owen S**, Gould D. Underwater seal chest drains: the patient's experience. *J Clin Nurs* 1997;**6**:215–25. [**IIb**]
34 **Parker LA**, Charnock GC, Delany DJ. Small bore catheter drainage and sclerotherapy for malignant pleural effusions. *Cancer* 1989;**64**:1218–21. [**III**]
35 **Morrison MC**, Mueller PR, Lee MJ, *et al*. Sclerotherapy of malignant pleural effusion through songraphically placed small-bore catheters. *AJR* 1992;**158**:41–3. [**III**]
36 **Seaton KG**, Patz EF Jr, Goodman PC. Palliative treatment of malignant pleural effusions: value of small-bore catheter thoracostomy and doxycycline sclerotherapy. *AJR* 1995;**164**:589–91. [**IIb**]
37 **Patz EF Jr**, McAdams HP, Erasmus JJ, *et al*. Sclerotherapy for malignant pleural effusions: a prospective randomized trial of bleomycin vs doxycycline with small-bore catheter drainage. *Chest* 1998;**113**:1305–11. [**Ib**]
38 **Clementsen P**, Evald T, Grode G, *et al*. Treatment of malignant pleural effusion: pleurodesis using a small percutaneous catheter. A prospective randomized study. *Respir Med* 1998;**92**:593–6. [**Ib**]
39 **Patz EF Jr**, McAdams HP, Goodman PC, *et al*. Ambulatory sclerotherapy for malignant pleural effusions. *Radiology* 1996;**199**:133–5. [**IIb**]
40 **Adler RH**, Sayek I. Treatment of malignant pleural effusion: a method using tube thoracostomy and talc. *Ann Thorac Surg* 1976;**22**:8–15. [**IIb**]
41 **Villanueva AG**, Gray AW Jr, Shahian DM, *et al*. Efficacy of short term versus long term tube thoracostomy drainage before tetracycline pleurodesis in the treatment of malignant pleural effusions. *Thorax* 1994;**49**:23–5. [**Ib**]
42 **Kennedy L**, Rusch VW, Strange C, *et al*. Pleurodesis using talc slurry. *Chest* 1994;**106**:342–6. [**III**]
43 **Robinson L A**, Fleming WH, Galbraith TA. Intrapleural doxycycline control of malignant pleural effusions. *Ann Thorac Surg* 1993;**55**:1115–21. [**III**]
44 **Tarver RD**, Broderick LS, Conces DJ. Reexpansion pulmonary edema. *J Thorac Imag* 1996;**11**:198–209. [**IV**]
45 **Mahfood S**, Hix WR, Aaron BL, *et al*. Reexpansion pulmonary edema. *Ann Thorac Surg* 1988;**45**:340–5. [**IV**]
46 **Nakamura H**, Ishizaka A, Sawafuji M, *et al*. Elevated levels of interleukin-8 and leukotriene B_4 in pulmonary edema fluid of a patient with reexpansion pulmonary edema. *Am J Respir Crit Care Med* 1994;**149**:1037–40. [**IV**]
47 **Pulsiripunya C**, Youngchaiud P, Pushpakom R, *et al*. The efficacy of doxycycline as a pleural sclerosing agent in malignant pleural effusion: a prospective study. *Respirology* 1996;**1**:69–72. [**IIb**]
48 **Wooten SA**, Barbarash RA, Strange C, *et al*. Systemic absorption of tetracycline and lidocaine following intrapleural instillation. *Chest* 1988;**94**:960–3. [**III**]
49 **Sherman S**, Grady KJ, Seidman JC. Clinical experience with tetracycline pleurodesis of malignant pleural effusions. *South Med J* 1987;**80**:716–9. [**III**]
50 **Whitwam JG**, Wang C. Sedation and sedoanalgesia. In: Whitwam J G. *Day-case anaesthesia and sedation*. London: Blackwell Scientific Publications, 1994: 262–74. [**IV**]
51 **McAlpine LG**, Hulks G, Thomson NC. Management of recurrent malignant pleural effusion in the United Kingdom: survey of clinical practice. *Thorax* 1990;**45**:699–701. [**IV**]
52 **Heffner JE**, Unruh LC. Tetracycline pleurodesis: adios, farewell, adieu. *Chest* 1992;**101**:64–6. [**IV**]
53 **Bayly TC**, Kisner DL, Sybert A, *et al*. Tetracycline and quinacrine in the control of malignant pleural effusions. A randomized trial. *Cancer* 1978;**41**:1188–92. [**Ib**]
54 **Landvater L**, Hix WR, Mills M, Siegel RS, *et al*. Malignant pleural effusion treated by tetracycline sclerotherapy. A comparison of single vs repeated instillation. *Chest* 1988;**93**:1196–8. [**Ib**]
55 **Martinez-Moragon E**, Aparicio J, Rogado MC, *et al*. Pleurodesis in malignant pleural effusions: a randomized study of tetracycline versus bleomycin. *Eur Respir J* 1997;**10**:2380–3. [**Ib**]
56 **Gravelyn TR**, Michelson MK, Gross BH, *et al*. Tetracycline pleurodesis for malignant pleural effusions. A 10-year retrospective study. *Cancer* 1987;**59**:1973–7. [**III**]
57 **Kessinger A**, Wigton RS. Intracavitary bleomycin and tetracycline in the management of malignant pleural effusions: a randomized study. *J Surg Oncol* 1987;**36**:81–3. [**Ib**]
58 **Evans TR**, Stein RC, Pepper JR, *et al*. A randomized prospective trial of surgical against medical tetracycline pleurodesis in the management of malignant pleural effusions secondary to breast cancer. *Eur J Cancer* 1993;**29A**:316–9. [**Ib**]
59 **Fentiman IS**, Rubens RD, Hayward JL. A comparison of intracavitary talc and tetracycline for the control of pleural effusions secondary to breast cancer. *Eur J Cancer Clin Oncol* 1986;**22**:1079–81. [**Ib**]
60 **McAlpine LG**, Kay JW, Thomson NC, *et al*. Tetracycline pleurodesis in malignant pleural effusion: a comparison of needle aspiration with intercostal tube drainage. *Thorax* 1995;**50**:437P. [**Ib**]
61 **Bethune N**. Pleural poudrage: new technique for deliberate production of pleural adhesions as a preliminary to lobectomy. *J Thorac Surg* 1935;**4**:251–61. [**IV**]
62 **Marom EM**, Patz EF Jr., Erasmus JJ, *et al*. Malignant pleural effusions: treatment with small-bore catheter thoracostomy and talc pleurodesis. *Radiology* 1999;**210**:277–81. [**IIb**]
63 **Thompson RL**, Yau JC, Donnelly RF, Gowan DJ, *et al*. Pleurodesis with iodized talc for malignant effusions using pigtail catheters. *Ann Pharmacother* 1998;**32**:739–42. [**IIb**]
64 **Webb WR**, Ozmen V, Moulder PV, *et al*. Iodized talc pleurodesis for the treatment of pleural effusions. *J Thorac Cardiovasc Surg* 1992;**103**:881–5. [**III**]
65 **Weissberg D**, Ben-Zeev I. Talc pleurodesis. Experience with 360 patients. *J Thorac Cardiovasc Surg* 1993;**106**:689–95. [**III**]
66 **Lynch TJ Jr**, Kalish L, Mentzer SJ, *et al*. Optimal therapy of malignant pleural effusions: report of a randomized trial of bleomycin, tetracycline and talc and a meta-analysis. *Int J Oncol* 1996;**8**:183–90. [**Ib**]
67 **Zimmer PW**, Hill M, Casey K, Harvey E, *et al*. Prospective randomized trial of talc slurry vs bleomycin in pleurodesis for symptomatic malignant pleural effusions. *Chest* 1997;**112**:430–4. [**Ib**]
68 **Yim AP**, Chung SS, Lee TW, *et al*. Thoracoscopic management of malignant pleural effusions. *Chest* 1996;**109**:1234–8. [**III**]
69 **Rinaldo JE**, Owens GR, Rogers RM. Adult respiratory distress syndrome following intrapleural installation of talc. *J Thorac Cardiovasc Surg* 1983;**85**:523–6. [**IV**]
70 **Ferrer J**, Villarino MA, Tura JM, *et al*. Talc preparations used for pleurodesis vary markedly from one preparation to another. *Chest* 2001;**119**:1901–5. [**IV**]
71 **Alberts DS**, Chen HSG, Mayersohn M, *et al*. Bleomycin pharmacokinetics in man II: Intracavitary administration. *Cancer Chemother Pharmacol* 1979;**2**:127–32. [**III**]
72 **Bitran JD**, Brown C, Desser RK, *et al*. Intracavitary bleomycin for the control of malignant effusions. *J Surg Oncol* 1981;**16**:273–7. [**III**]
73 **Ostrowski MJ**, Halsall GM. Intracavitary bleomycin in the management of malignant effusions: a multicenter study. *Cancer Treatment Reports* 1982;**66**:1903–7. [**III**]
74 **Ruckdeschel JC**, Moores D, Lee JY, *et al*. Intrapleural therapy for malignant pleural effusions. A randomized comparison of bleomycin and tetracycline. *Chest* 1991;**100**:1528–35. [**Ib**]
75 **Hartman DL**, Gaither JM, Kesler KA, *et al*. Comparison of insufflated talc under thoracoscopic guidance with standard tetracycline and bleomycin pleurodesis for control of malignant pleural effusions. *J Thorac Cardiovasc Surg* 1993;**105**:743–7. [**Ib**]
76 **Goff BA**, Mueller PR, Muntz HG, *et al*. Small chest-tube drainage followed by bleomycin sclerosis for malignant pleural effusions. *Obstet Gynecol* 1993;**81**:993–6. [**III**]
77 **Hsu WH**, Chiang CD, Chen CY, *et al*. Ultrasound-guided small-bore Elecath tube insertion for the rapid sclerotherapy of malignant pleural effusion. *Jpn J Clin Oncol* 1998;**28**:187–91. [**III**]
78 **Mansson T**. Treatment of malignant pleural effusion with doxycycline. *Scand J Infect Dis* 1988;**53**(Suppl):29–34. [**III**]

79 **Heffner JE**, Standerfer RJ, Torstveit J, *et al*. Clinical efficacy of doxycyline for pleurodesis. *Chest* 1994;**105**:1743–7. [**III**]
80 **Prevost A**, Nazeyrollas P, Milosevic D, *et al*. Malignant pleural effusions treated with high dose intrapleural doxycycline: clinical efficacy and tolerance. *Oncol Reports* 1998;**5**:363–6. [**III**]
81 **Hatta T**, Tsubuota N, Yoshimura M, *et al*. Effect of intrapleural administration of minocycline on postoperative air leakage and malignant pleural effusions. *Kyobu Geka* 1990;**43**:283–6. [**III**]
82 **Light RW**, Sassoon CS, Vargas FS, *et al*. Comparison of the effectiveness of tetracycline and minocycline as pleural sclerosing agents in rabbits. *Am Rev Respir Dis* 1992;**145**:A868. [**III**]
83 **Webb HE**, Oaten SW, Pike CP. Treatment of malignant ascitic and pleural effusions with Corynebacterium parvum. *BMJ* 1978;1:338–40. [**III**]
84 **McLeod DT**, Calverley PM, Millar JW, *et al*. Further experience of Corynebacterium parvum in malignant pleural effusion. *Thorax* 1985;**40**:515–8. [**IIb**]
85 **Millar JW**, Hunter AM, Horne NW. Intrapleural immunotherapy with Corynebacterium parvum in recurrent malignant pleural effusions. *Thorax* 1979;**35**:856–8. [**Ib**]
86 **Leahy BC**, Honeybourne D, Brear SG, *et al*. Treatment of malignant pleural effusions with intrapleural Corynebacterium parvum or tetracycline. *Eur J Respir Dis* 1985;**66**:50–4. [**Ib**]
87 **Ostrowski MJ**, Priestman TJ, Houston RF, *et al*. A randomized trial of intracavitary bleomycin and Corynebacterium parvum in the control of malignant pleural effusions. *Radiother Oncol* 1989;**14**:19–26. [**Ib**]
88 **Foresti V**. Intrapleural Corynebactrium parvum for recurrent malignant pleural effusions. *Respiration* 1995;**62**:21–6. [**III**]
89 **Bilaceroglu S**, Cagirici U, Perim K, *et al*. Corynebacterium parvum pleurodesis and survival is not significantly influencd by pleural pH and glucose level. *Monaldi Arch Chest Dis* 1998;**53**:14–22. [**IIb**]
90 **Rosso R**, Rimoldi R, Salvati F, *et al*. Intrapleural natural beta interferon in the treatment of malignant pleural effusions. *Oncology* 1988;**45**:253–6. [**III**]
91 **Lissoni P**, Barni S, Tancini G, *et al*. Intracavitary therapy of neoplastic effusions with cytokines: comparison among interferon alpha, beta and interleukin-2. *Supportive Care in Cancer* 1995;**3**:78–80. [**Ib**]
92 **Davis M**, Williford S, Muss HB, *et al*. A phase I-II study of recombinant intrapleural alpha interferon in malignant pleural effusions. *Am J Clin Oncol* 1992;**15**:328–30. [**III**]
93 **Goldman CA**, Skinnider LF, Maksymiuk AW. Interferon instillation for malignant pleural effusions. *Ann Oncol* 1993;**4**:141–5. [**III**]
94 **Wilkins HE**, Connolly MM, Grays P, *et al*. Recombinant interferon alpha-2b in the management of malignant pleural effusions. *Chest* 1997;**111**:1597–9. [**IIb**]
95 **Viallat JR**, Boutin C, Rey F, *et al*. Intrapleural immunotherapy with escalating doses of interleukin-2 in metastatic pleural effusions. *Cancer* 1993;**71**:4067–71. [**III**]
96 **Masotti A**, Fumagalli L, Morandini GC. Intrapleural administration of recombinant interleukin-2 in non-small cell lung cancer with neoplastic pleural effusion. *Monaldi Arch Chest Dis* 1997;**52**:225–8. [**III**]
97 **Rusch VW**, Figlin R, Godwin D, *et al*. Intrapleural cisplatin and cytarabine in the management of malignant pleural effusions: a Lung Cancer Study Group trial. *J Clin Oncol* 1991;**9**:313–9. [**IIb**]
98 **Morales M**, Exposito MC. Intrapleural mitoxantrone for the palliative treatment of malignant pleural effusions. *Supportive Care in Cancer* 1995;**3**:147–9. [**III**]
99 **Aasebo U**, Norum J, Sager G, *et al*. Intrapleurally instilled mitoxantrone in metastatic pleural effusions: a phase II study. *J Chemother* 1997;**9**:106–11. [**III**]
100 **Lorch DG**, Gordon L, Wooten S, *et al*. Effect of patient positioning on distribution of tetracycline in the pleural space during pleurodesis. *Chest* 1988;**93**:527–9. [**III**]
101 **Dryzer SR**, Allen ML, Strange C, *et al*. A comparison of rotation and nonrotation in tetracycline pleurodesis. *Chest* 1993;**104**:1763–6. [**Ib**]
102 **Sahn SA**. Pleural diseases related to metastatic malignancies. *Eur Respir J* 1997;**10**:1907–13. [**IV**]
103 **Yim AP**, Chan AT, Lee TW, *et al*. Thoracoscopic talc insufflation versus talc slurry for symptomatic malignant pleural effusion. *Ann Thorac Surg* 1996;**62**:1655–8. [**Ib**]
104 **Lynch TJ Jr**. Management of malignant pleural effusions. *Chest* 1993;**103**(Suppl):385–9S. [**IV**]
105 **Jones FL Jr**. Subcutaneous implantation of cancer: a rare complication of pleural biopsy. *Chest* 1970;**57**:189–90. [**IV**]
106 **Berger L**, Dargan EL, Huang BL. Dissemination of cancer cells by needle biopsy of the lung. *J Thorac Cardiovasc Surg* 1972;**63**:430–2. [**IV**]
107 **Kumar UN**, Varkey B. Case report: subcutaneous metastasis. Rare complication of drainage of malignant pleural fluid. *Postgrad Med* 1976;**60**:253–5. [**IV**]
108 **Yim AP**. Port-site recurrence following video-assisted thoracoscopic surgery. *Surg Endosc* 1995;**9**:1133–5. [**IV**]
109 **Boutin C**, Rey F, Viallat JR. Prevention of malignant seeding after invasive diagnostic procedures in patients with pleural mesothelioma. *Chest* 1995;**108**:754–8. [**Ib**]
110 **Tillet WS**, Sherry S. The effect in patients of streptococcal fibrinolysin (streptokinase) and streptococcal deoxyribonuclease on fibrinous, purulent and sanguinous pleural exudations. *J Clin Invest* 1949;**28**:173–90. [**IIb**]
111 **Godley PJ**, Bell RC. Major hemorrhage following administration of intrapleural streptokinase. *Chest* 1984;**86**:486–7. [**IV**]
112 **Jerjes-Sanchez C**, Ramirez-rivera A, Elizalde JJ, *et al*. Intrapleural fibrinolysis with streptokinase as an adjunctive treatment in hemothorax and empyema. *Chest* 1996;**109**:1514–9. [**IIb**]
113 **Davies CWH**, Traill ZC, Gleeson FV, *et al*. Intrapleural streptokinase in the management of malignant multiloculated pleural effusions. *Chest* 1999;**115**:729–33. [**III**]
114 **Gilkeson RC**, Silverman P, Haaga JR. Using urokinase to treat malignant pleural effusions. *AJR* 1999;**173**:781–3. [**III**]
115 **Menzies R Charbonneau M**. Thoracoscopy for the diagnosis of pleural disease. *Ann Intern Med* 1991;**114**:271–6. [**IIb**]
116 **Harris R J**, Kavuru MS, Rice TW, *et al*. The diagnostic and therapeutic utility of thoracoscopy. *Chest* 1995;**108**:828–41. [**IV**]
117 **Loddenkemper R**. Thoracoscopy: state of the art. *Eur J Respir* 1998;**11**:213–21. [**IV**]
118 **Canto A**, Blasco E, Casillas M, *et al*. Thoracoscopy in the diagnosis of pleural effusion. *Thorax* 1977;**32**:550–4. [**III**]
119 **Yim AP**, Chung SS, Lee TW, *et al*. Thoracoscopic management of malignant pleural effusions. *Chest* 1996;**109**:1234–8. [**IV**]
120 **Viallat JR**, Rey F, Astoul P, *et al*. Thoracoscopic talc poudrage pleurodesis for malignant effusions. A review of 360 cases. *Chest* 1996;**110**:1387–93. [**III**]
121 **Colt HG**. Therapeutic thoracoscopy. *Clin Chest Med* 1998;**19**:383–94. [**IV**]
122 **Viskum K**, Enk B. Complications of thoracoscopy. *Poumon Coeur* 1981;**37**:25–8. [**IV**]
123 **Milanez de Campos JR**, Vargas FS, Werebe EC, *et al*. Thoracoscopy talc poudrage. A 15-year experience. *Chest* 2001;**119**:801–6. [**IV**]
124 **Putnam JB**, Light RW, Rodriguez RM, *et al*. A randomized comparison of indwelling pleural catheter and doxycycline pleurodesis in the management of malignant pleural effusions. *Cancer* 1999;**86**:1992–9. [**Ib**]
125 **Warren WH**, Faber LP. Clinical experience with Pleurx catheters for malignant pleural effusions. *Chest* 2000;**118**(Suppl):130S. [**III**]
126 **Little AG**, Ferguson MK, Golomb HM, *et al*. Pleuroperitoneal shunting for malignant pleural effusions. *Cancer* 1986;**58**:2740–3. [**III**]
127 **Wong PS**, Goldstraw P. Pleuroperitoneal shunts. *Br J Hosp Med* 1993;**50**:16–21. [**IV**]
128 **Petrou M**, Kaplan D, Goldstraw P. Management of recurrent malignant pleural effusions. The complementary role of talc pleurodesis and pleuroperitoneal shunting. *Cancer* 1995;**75**:801–5. [**III**]
129 **Lee KA**, Harvey JC, Reich H, *et al*. Management of malignant pleural effusions with pleuroperitoneal shunting. *J Am Coll Surg* 1994;**178**:586–8. [**III**]
130 **Martini N**, Bains MS, Beattie EJ Jr. Indications for pleurectomy in malignant effusion. *Cancer* 1975;**35**:734–8. [**III**]
131 **Fry WA**, Khandekar JD. Parietal pleurectomy for malignant pleural effusions. *Ann Surg Oncol* 1995;**2**:160–4. [**III**]
132 **Waller DA**, Morritt GN, Forty J. Video-assisted thoracoscopic pleurectomy in the management of malignant pleural effusion. *Chest* 1995;**107**:1454–6. [**IIb**]